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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTIBODIES LACKING VACUOLAR TARGETING SIGNAL PEPTIDE AND CAPABLE OF BINDING J-CHAIN

(57) Abstract: The application discloses a method of making an antibody molecule, the antibody containing an immunoglobulin heavy chain comprising a $\alpha 3$ domain or a μ domain, the method comprising: (a) Providing a nucleotide sequence encoding the immunoglobulin heavy chain; (b) Modifying the nucleotide sequence in the region of the nucleotide sequence encoding the C-terminus 18 amino acids of the completed heavy chain to remove, or reduce the effectiveness of, one or more vacuolar targeting signal sequences to form a modified nucleotide sequence; (c) Inserting the modified nucleotide sequence into a host cell; and (d) Causing the host cell to express the modified nucleotide sequence to form the modified antibody heavy chain and secrete the modified antibody heavy chain from the host cell. This improves the secretion of the antibody from, for example, plant cells. Methods of adding J-chain binding activity to antibodies are also provided. The modified antibodies and their use is also disclosed.

WO 2004/046190 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/04983

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K16/00 C12N15/82

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data, PAJ, SEQUENCE SEARCH, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHOUTEN A ET AL: "THE C-TERMINAL KDEL SEQUENCE INCREASES THE EXPRESSION LEVEL OF A SINGLE-CHAIN ANTIBODY DESIGNED TO BE TARGETED TO BOTH THE CYTOSOL AND THE SECRETORY PATHWAY IN TRANSGENIC TOBACCO" PLANT MOLECULAR BIOLOGY, NIJHOFF PUBLISHERS, DORDRECHT, NL, vol. 30, 1996, pages 781-793, XP000677225 ISSN: 0167-4412 Paragraph "discussion" --- -/--	1-3, 14-18, 27-32

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/04983

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROBINSON EA ET AL.: "Amino acid sequence of a mouse myeloma immunoglobulin heavy chain (MOPC 47A) with a 100-residue deletion." THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 254, no. 22, 1979, pages 11418-11430, XP002276487 abstract	19
Y	----- ALESSANDRO VITALE , MAARTEN J CHRISPEELS: "Sorting of proteins to the vacuoles of plant cells" BIOESSAYS, vol. 14, no. 3, 1992, pages 151-160, XP008029495 First paragraph in "concluding comments"	4-24,27, 30-33
Y	----- L. FRIGERIO ET AL.: "Assembly, secretion, and vacuolar delivery of a hybrid immunoglobulin in plants" PLANT PHYSIOLOGY, vol. 123, 2000, pages 1483-1493, XP001189719 cited in the application page 1489, left-hand column, paragraphs 2,3	4-27, 30-33
Y	----- MATSUOKA K ET AL.: "Cis-element of protein transport to the plant vacuoles" JOURNAL OF EXPERIMENTAL BOTANY, vol. 50, no. 331, 1999, pages 165-174, XP000118956 page 168, right-hand column, paragraph 3 -----	25,26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/04983

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 28,29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-33 all partially
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-33 all partially

Present claims 1-33 relate to a compound/method defined by reference to a desirable characteristic or property, namely:

- remove or reduce the effectiveness of one or more vacuolar targeting signal sequences,
- a method of adding J-chain binding capability,
- an antibody lacking one or more targeting signals,

The claims cover all compounds/methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound/method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely: an antibody containing an alpha3 domain lacking of vacuolar targeting signal sequence, being capable of polymerisation, produced by a transgenic plant or yeast and having a tailpiece as claimed in claim 7; so that, claim 20 which is broader than the method claims 1-17 has been restricted in the same way.

In view of the wording of the claim 7 ("A method according to any preceding claim wherein one nucleotides encoding an amino acid sequence..." has been read as follows "A method according to any preceding claim wherein the modified amino sequence...") presently on file, which render it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise), namely an antibody containing an alpha3 domain lacking of vacuolar targeting signal sequence, being capable of polymerisation, produced by a transgenic plant or yeast and having a tailpiece as claimed in claim 7; so that, claim 20 which is broader than the method claims 1-17 has been restricted in the same way.

Entity claims 25 and 26 indicate a dependency "according to any preceding claim" including method claim 1, which makes no sense. Thus the dependency has been restricted to independent entity claims 18-20.

The wording of present claim 20 is unclear : "an antibody capable of binding J-chain" could be interpreted as 1) an antibody capable of binding via its antigen-binding sites of the VH and VL regions to J-chain or, alternatively, 2) an antibody capable of binding J-chain via the antibody's constant region. The latter has been assumed. In view of said

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

wording present claim 20, which render it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise), namely : an antibody containing an alpha3 domain lacking of vacuolar targeting signal sequence, being capable of polymerisation, produced by a transgenic plant or yeast and having a tailpiece as claimed in claim 7; so that, claim 20 which is broader than the method claims 1-17 has been restricted in the same way.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.